The Specification

The Office Action states that the status of the U.S. applications disclosed in the specification needs to be updated. Applicants have met this objection by amending the first sentence in the specification to recite: This application is a continuation of application Serial No. 08/757,958, filed November 25, 1996, now abandoned, which is a continuation application of Serial No. 08/061,699, filed May 12, 1993, now abandoned.

35 U.S.C. §132

The amendment filed September 18, 1997, has been objected to under 35 U.S.C. §132, as introducing new matter. Applicants respectfully traverse this rejection.

The Office Action states that SEQ ID NO:8 is new matter because "Xaa" as used in the amino acid sequence encompasses an "unknown or other" amino acid and that the Sequence Listing filed September 18, 1997, does not define Xaa as used in SEQ ID NO:8.

While applicants believe that there is support in the specification, and that it would be known to one skilled in the art, that the "." in the consensus sequence of Fig. 2 encompasses "unknown or other" amino acids, applicants have amended the Sequence Listing to overcome the objection so as to expedite prosecution of the application.

The Sequence Listing has been amended to include section

(ix) such that Xaa at position 1 represents A, S, E, Q, G, H, T, D, R, K, N or V, at position 3 represents Y, Q, R, H, T, N, I, L or S, at position 8 represents A, Q, V, I, N, T, S, K, E, R or H, at position 14 represents N, R, H, K, A, Y, S, F, L, Q or T, at position 16 represents F, V, I or L, at position 17 represents V, A, T, S or P, at position 21 represents R, S, G, T, N, M, A, L, T, Q, D, K or E, at position 22 represents S, P, L, V, H, R, Y, Q, T or A, at position 24 represents A, S or P, and at position 27 represents N, D, K, R, T or E. Support for this amendment is found in Fig. 2 which discloses that the "." positions in the consensus sequence indicated at the top of Fig. 2, include the specific amino acids recited in the subsequent 90 sequences disclosed in Fig. 2. The Office Action itself, at page 3, lines 7-9, acknowledges that "Figure 2 possibly discloses that the "." position in the consensus sequence was found to be a particular amino acid recited in the 90 sequences disclosed in Figure 2." See also Example 1.

In sum, now that the amino acid positions designated "." have been limited to certain specifically cited amino acid residues, the 35 U.S.C. §132 objection should be withdrawn.

35 U.S.C. §112, first paragraph

Claims 40-42, 45, 48, 49, 52 and 53 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter

which was not described in the specification. Applicants respectfully traverse this rejection. The Office Action states that there is no support in the specification for SEQ ID NO:8 in claim 40. Applicants have amended the Sequence Listing to overcome this rejection, as discussed above in the 35 U.S.C. §132 section.

Claims 40-42, 45, 48, 49, 52 and 53 have also been rejected under 35 U.S.C. §112, first paragraph in that there is no support for the recitation of "wherein the amino acid sequence motif is the only sequence corresponding to a hypervariable domain of hepatitis C virus." Applicants respectfully traverse this rejection. The written description requirement requires that the invention be described in such a way that it is clear that the applicant invented what is claimed. See, e.g., In re Benno, 768 F.2d 1340 (Fed. Cir. 1985). The specification teaches that the average rate of change of the HCV genome within a single persistently-infected individual is about 1-2 X 10^3 nt changes/site/year, but that there is a much higher rate of change at the extreme 5'-terminus of the gene encoding the N-terminus of the E2/NS1 glycoprotein, called the E2 "hypervariable" region. This E2 hypervariable region spans amino acids about 384-414. SEQ ID NO:8 is within this hypervariable region. See, e.g., page 6, lines 14-28; page 7, lines 21-23; page 7, lines 24-26; page 50, lines 3-8; Fig. 1; and Fig. 2. Thus, there is support for

the phrase cited above.

Claims 48 and 49 have also been rejected under 35 U.S.C. §112, first paragraph in that there is no support for the recitation of "comprising all or portion of a particle forming protein" or for the recitation of "fused with an amino acid sequence encoding all or portion of a particle forming protein." Applicants respectfully traverse this rejection. The written description requirement requires that the invention be described in such a way that it is clear that the applicant invented what is claimed. See, e.g., In re Benno, 768 F.2d 1340 (Fed. Cir. 1985). The specification states at page 20, line 28 through page 21, line 10:

> The immunogenicity of the antigens comprised of the SLF--G motif may also be enhanced by preparing them in eukaryotic systems fused with or assembled with particle-forming proteins such as, for example, that associated with hepatitis B surface antigen. See, e.g., U.S. Patent No. 4,722,840. These constructs may also be expressed in mammalian cells such as CHO cells using an SV40-dihydrofolate reductase vector (Michelle et al. (1984)). (Emphasis added).
>
> In addition, portions of the particle-forming protein coding sequence may be replaced with codons encoding the SLF--G epitope from an HCV hypervariable domain. In this replacement, regions which are not required to mediate the aggregation of the units to form immunogenic particles in yeast or mammals can be deleted, thus eliminating additional HBV antigenic sites from competition with the HCV epitope(s). (Emphasis added).

See also the specification at page 14, lines 8-19:

> The amino acid sequence comprising the HCV epitope may be linked to another polypeptide (e.g., a carrier protein), either by covalent attachment or by expressing a fused polynucleotide to form a fusion protein. ...If desired, one may employ a substantially full-length HCV protein as the carrier, multiplying the number of immunogenic epitopes. Alternatively, the amino acid sequence from the HCV epitope may be linked at the amino terminus and/or carboxy terminus to a non-HCV amino acid sequence, thus the polypeptide would be a fusion polypeptide. Analogous types of polypeptides may be constructed using epitopes from other designated viral proteins. (Emphasis added).

Thus, the specification discloses antigens comprising the SLF--G motif which further comprise all or a portion of a particle forming protein, or the SLF--G motif which is fused with an amino acid sequence encoding all or a portion of a particle forming protein. In addition, the polypeptides of the claims, i.e., SEQ ID NO:8 (delineated by the amended Sequence Listing as discussed above), are antigens which "comprise the SLF--G motif" (amino acid residues 18-23 of SEQ ID NO:8), and thus are clearly covered by the section of the specification cited above. Moreover, each specific antigen which "comprises the SLF--G motif" that is specifically disclosed elsewhere in the specification (e.g., SEQ ID NO:8), does not need to be relisted every time the phrase "an antigen which comprises the SLF--G motif" is recited in the specification. It would be clear to anyone skilled in the art that SEQ ID NO:8, which is taught in the specification, is included in the phrase "an antigen which comprises the SLF--G motif," which is cited above.

Claim 52 has also been rejected under 35 U.S.C. §112, first paragraph in that there is no support for the recitation of "immunologic composition." Applicants respectfully traverse this rejection. The written description requirement requires that the invention be described in such a way that it is clear that the applicant invented what is claimed. See, e.g., In re Benno, 768 F.2d 1340 (Fed. Cir. 1985). The claim recites an "immunogenic composition," not an "immunologic composition." Support for an "immunogenic composition" is found in the specification. See, e.g.,:

> In one embodiment of the invention, the immunogenic compositions comprised of a polypeptide having a region that binds an antibody directed to an antigenic determinant containing the SLF--G motif is used for vaccine applications to stimulate immune responsiveness to the HCV antigenic determinant(s) containing the motif. (Emphasis added). (Page 19, lines 2-5).

> The immunogenic compositions (e.g., the antigen, pharmaceutically acceptable carrier, and adjuvant) typically will contain diluents, such as water, saline, glycerol, ethanol, etc. (Emphasis added). (Page 22, lines 21-23).

> Typically, the immunogenic compositions are prepared as injectables... (Emphasis added). (Page 22, line 25).

> Immunogenic compositions used as vaccines comprise an immunologically effective amount of the antigenic polypeptides, as well as any other of the above mentioned components, as needed. (Emphasis added). (Page 23, lines 1-3).

> The immunogenic compositions are conventionally administered parenterally, e.g., by injection, either subcutaneously or intramuscularly. (Emphasis added). (Page 23, lines 12-13).

Claims 40-42, 45, 48, 49, 52 and 53 have also been rejected under 35 U.S.C. §112, first paragraph in that the specification is not enabled for the claimed peptides wherein the peptides are "immunogenic." The Office Action states that it would require undue experimentation to determine which peptides encompassed by the claimed invention are and are not immunogenic. Applicants respectfully traverse this rejection. See, e.g., Ex Parte Forman, 230 U.S.P.Q. 546 (Bd. App. 1986). The specification states that "immunogenic" means the ability to elicit a cellular and/or humoral immune response). (Page 14, lines 1-2). Methods for determining the immunogenicity of a peptide were well known to those skilled in the art at the time that this application was filed. The specification specifically teaches methods for determining immunogenicity of the peptides of this invention. See, e.g., page 4, line 23 through page 5, line 12; page 8, lines 3-8; page 23, line 26 through page 24, line 23; page 25, line 24 through page 26, line 14; Example 2, page 30 through page 37; and Example 4, page 42. These methods were will known in the art, are straight-forward, standard procedures, and do not require undue experimentation. In addition to the teachings provided in the specification, the attached declaration of Dr. Amy Weiner (Attachment B), prepared and filed in application Serial No. 08/438,183, is made of record herein. Moreover, see Attachment A, which teaches that broadly cross-reacting antibodies to HVR1 can be induced by consensus sequence peptides.

Summary

In view of the above, it is respectfully submitted that the claims are in condition for allowance and such action is requested.

Please direct all correspondence relating to this application to Alisa A. Harbin, Esq., Chiron Corporation, Intellectual Property-R440, P.O. Box 8097, Emeryville, CA 94662-8097, telephone number (510) 923-2708.

Please charge any fees that may be required to Deposit Account No. 19-0733.

Respectfully submitted,

By: Helen Greer

Helen Greer, Reg. No. 36,816
BANNER & WITCOFF, LTD.
28 State Street
Boston, MA 02109
Tel (617) 227-7111

September 28, 1998

Attachment A

The Fifth
International Meeting of Hepatitis C
Virus and Related Viruses, Molecular
Virology and Pathogenesis, Venice,
Italy, June 25-28, 1998; Poster 0-043

IMMUNOREACTIVITY AND IMMUNOGENICITY STUDIES ON EPITOPES IN THE E2 HVR1 OF THE HEPATITIS C VIRUS

D. Chien, P. Archangel, Q.-L. Choo, S. Coates, J. Kansopon, J. Lau*, S. Abrignani, G. Kuo, M. Houghton, A. Weiner. Chiron Corporation, Emeryville, CA USA; *University of Florida, Gainesville, FL

Previous studies identified linear B cell epitopes in the amino terminus of the HCV E2 glycoprotein which appear to mutate as a result of immune selective pressure. Although not absolutely proven, considerable evidence suggests that virus neutralizing epitopes reside between amino acids 390-410. Data from in vitro virus neutralization studies in tissue culture cell lines and in chimpanzees support the notion that virus neutralizing antibodies are isolate specific. In order to determine to what extent cross-reacting (and potentially cross-neutralizing) antibodies to epitopes between aa390-410 exist, we compared the immunoreactivity of an isolate specific HVR1 peptide with two type 1 consensus sequence peptides (CSPs) in paid blood donors and patients with chronic type 1, 2 or 3 HCV infections. Polyclonal rabbit antisera was raised against the HCV-1 HVR1 (390-410) and two different consensus HVR1 sequence peptides for immunogenicity studies.

Our results indicate that: (1) There is a substantially higher degree of sera which react to CSPs than to the isolate-specific HVR1 peptide in the populations studied and (2) CSPs can induce antibodies which not only react with type 1a and 1b peptides but also to a conformational, recombinant type 1a (HCV-1) and type 1b (HCV-J) E2 antigen. In contrast, anti-HCV-1 HVR1 specific antibodies strongly reacted with the HCV-1 E2 antigen but was only borderline reactive with the HCV-J E2 antigen. Rabbit anti-HVR1 antisera are being tested in a neutralizing of binding (NOB) assay to attempt to correlate immunoreactivity with potential neutralizing activity.

In conclusion, broadly cross-reacting antibodies to the HVR1 can be induced by CSPs and may enhance vaccine preparations.

Attachment B

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of	Group Art Unit 1817
Amy Weiner, et al.	Examiner: B. Prickril
Serial No. 08/438, 183	Atty. Docket No. 02441.58524
Filed: May 9, 1995	

For: **CONSERVED MOTIF OF HEPATITUS C VIRUS E2/NS1 REGION**

DECLARATION UNDER 37 C.F.R. §1.132

Honorable Assistant Commissioner
for Patents
Washington, D.C. 20231

I, Amy Weiner, hereby declare the following:

1. I am presently a Senior Scientist in the area of Non-A, Non-B hepatitis research at Chiron Corporation in Emeryville, California. A copy of my curriculum vitae, describing my background and qualifications, is attached to this Declaration.

2. During the last twelve (12) years I have conducted research in viral hepatitis at Chiron Corporation. During this time I have been directly involved in the research supporting HCV diagnostics and vaccine development and I am a co-inventor of the above-referenced patent application.

3. I have known and am familiar with Dr. Chien's work submitted herewith.

4. The data obtained in Dr. Chien's experiments demonstrate that HCV antibodies have cross reactivity to a HCV peptide which is described using the formula recited in the present invention.

5. In Dr. Chien's experiment, seventeen (17) HCV antibody-positive human serum samples were tested for their binding activity to a HCV peptide of amino acid 390-410, *i.e.*, GSAARTTSGFVSLFAPGAKQN. Seven (7) HCV antibody-negative human serum samples were also included in the test as negative controls. As shown in Sheet 1 (Exhibit 1), fourteen (14) out of seventeen (17) HCV antibodies bound to the peptide described above. None of the negative controls showed any above background binding activity.

6. It is known that each HCV infected individual is most likely to have different HCV isolates with variant HCV sequences. Therefore, Dr Chien's experiment demonstrated that antibodies against a HCV peptide with a particular sequence can cross react with other HCV peptides or isolates having other sequences.

7. I am familiar with the report of Hattori et al., at the 4th International Meeting on Hepatitis C Virus and Related Viruses, held in Kyoto, Japan during March 6-10, 1997. I have reviewed the full text of the Hattori et al. poster presented at the meeting. An abstract of the poster is attached (Exhibit 2). My notes with verbatim quotations from the poster is also attached (see Exhibit 3).

8. Hattori et al. reported that one-hundred-and-eight (108) HCV infected human serum samples were tested for binding activity against five (5) different fusion proteins containing HCV sequences of amino acid 384-410 (see Exhibit 3, Clone 1-5). As stated in Results B, "each fusion proteins reacted with 36.1-59.3% of HCV infected patients..." (See Exhibit 3).

9. The experimental results reported by Hattori et al also demonstrate that HCV antibodies have cross-reactivity to HCV peptide variants or isolates.

10. The results obtained both by Dr. Chien and Hattori et al support the conclusion that

peptides which include sequences of this invention induce antibodies capable of cross-reacting with HCV peptides or isolates.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4/22/97
Date

Amy J. Weiner

CURRICULUM VITAE

AMY J. WEINER

BUSINESS ADDRESS

Chiron Corporation
4560 Horton Street
Emeryville, CA 94608
Phone: 510/420-4785
Fax: 510/655-9910 or 658-0329

EDUCATION

1976 A.B. Brown University, honors in biology

1983 Ph.D. Program in Molecular, Cellular and Development Biology
Indiana University

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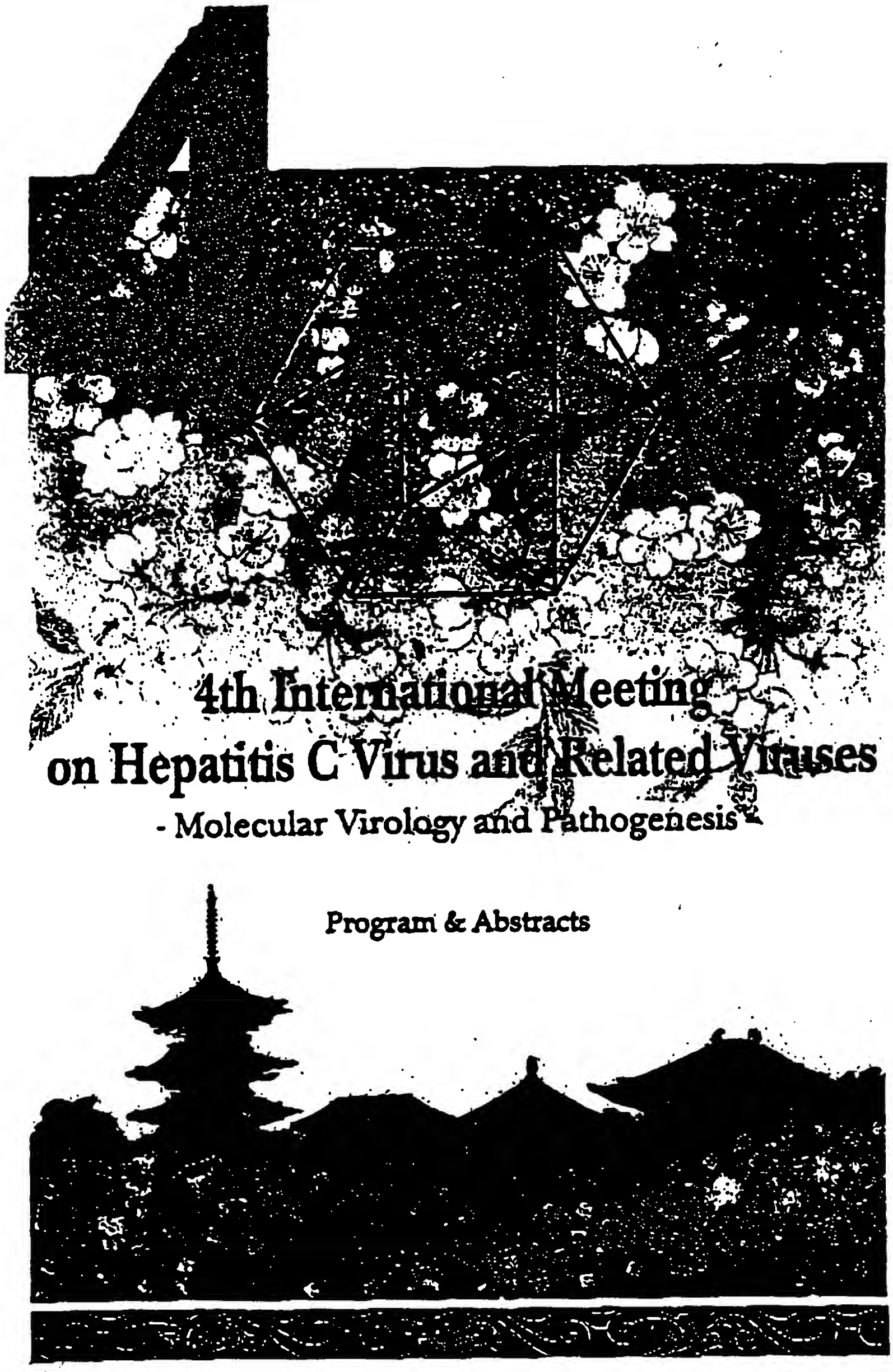
E2 HYPERVARIABLE REGION PEPTIDE

2ug/well peptide n 2ug/w ll Streptavidin Costar high binding plates

Paid donors		
	O.D.	
84-016953	2.686	+
96727	0.365	+
FF25905	0.519	+
FF25946	3.205	+
FF25912	1.506	+
84-017786	2.352	+
FF25934	1.852	+
FF25910	3.090	+
LL57366	1.832	+
FF25926	0.261	-
FF25879	0.049	-
96696	2.906	+
LL57382	0.535	+
LL57385	0.548	+
84-017623	0.851	+
LL57406	0.204	-
LL57454	3.275	+

r1	0.068
r2	0.104
r3	0.041
r4	0.064
r5	0.070
r6	0.115
r7	0.067

Peptide	aa sequence
#3	Biotin-Ahx-GSAARTTSGFVSLFAPGAKQN-COOH (consensus)



4th International Meeting on Hepatitis C Virus and Related Viruses

- Molecular Virology and Pathogenesis

Program & Abstracts

March 6-10, 1997

Kyoto International Conference Hall (KICH)

Kyoto, Japan

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CROSS-REACTIVITY OF ANTI-HYPERVARIABLE REGION ANTIBODY OF HCV INFECTED PATIENTS

M. Hattori[1], K. Yoshioka[1], T. Aiyama[1], K. Iwata[1], M. Yano[1], Y. Terasawa[1], M Ishigami[1], and S Kakumu[2].
Third Department of Internal Medicine, Nagoya University School of Medicine, Nagoya[1], First Department of Internal Medicine, Aichi Medical University, Aichi[2], Japan.

Several findings have been suggesting that antibody to the hypervariable region (HVR) of HCV has neutralizing activity. The patients infected with HCV have been shown to have anti-HVR antibody whose activity differs considerably from patient to patient. In order to clarify to what extent anti-HVR antibody of a patient cross-reacts with HVR obtained from the other patients, we assessed the cross-reactivity of anti-HVR antibody with 24 GST fusion proteins of HVR obtained from 12 patients by Western blot. The sera of patients reacted with 3-24 fusion proteins. The sera of two patients which did not react with the fusion proteins obtained from their own sera cross-reacted with 5 or 11 fusion proteins. These results indicate that there is considerable cross-reactivity of anti-HVR antibody despite the variability of amino acid sequences of HVR.

In addition, we selected 5 fusion proteins and assessed the reactivity of sera of 108 patients with these fusion proteins. Each fusion proteins reacted with 39-64 sera. 23 sera did not react with any of the five fusion proteins. With the three fusion proteins (one was genotype 1b and two were genotype 2a), sera of the patients infected with genotype 2a were significantly more frequently reactive than those infected with genotype 1b, while, with the other two fusion proteins (genotype 1b), there was no difference between genotypes. These results indicate that anti-HVR antibody is more frequently induced in the patients infected with genotype 2a than those with genotype 1b, and that the cross reactivity of anti-HVR antibody is not limited within genotypes.

EXHIBIT 3

TITLE Cross Reacting anti-HVR Ab in patients (cross genotype)

From Page N

Confirms our data see p.116 -- in patients; except our data used a consensus sequence to find antibodies rather than individual sequences (see p.116). Also the data below used a protein from aa 384-410. These can give evidence for establishing Ab antibodies to aa 390-410.

#306

Cross-reactivity of anti-hypervariable region antibody of HCV infected patients.

M. Hattori[1], K. Yoshioka[1], T. Aiyama[1], K. Iwata[1], M. Yano[1], Y. Terasawa[1], M. Ishigami[1], and S. Kakumu[2].
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Protocol:

GST-384-410 (pGEX-25) ➜ DH5α+(IPTG)

⬇ fusion protein purified on Glutathione beads

⬇

Westerns w/ patient sera

Results

A. 42 clones (#1-4 for each of 21 patients).
"All the patients sera cross-reacted with variable percentages of HVR proteins obtained from the other patients (7.1-78.6%). Sera often reacted with the HVR proteins from the different genotype."

B. Five clones expressed reacted with 108 HCV infected patients (see protocol above).
"Each fusion proteins reacted with 36.1-59.3% of HCV infected patients; 64 sera reacted with fusion protein 39-1 (genotype 2a), 61 with 132-36 (genotype 1b), 46 with 63-4 (genotype 1b), 44 with 37-1 (genotype 2a) and 39 with 66-4 (genotype 1b). 23 sera did not react with any of the 5 fusion proteins."

Conclusions

"HCV-infected patients sera cross-reacted with different HVR proteins obtained from the others at variable rate. Cross-reactivity of anti-HVR antibodies was not limited within genotypes.".

Clone	384...401	407...410
1. 132-36	...RLFAPGS...	
2. 66-4	...ALFTKGP...	
3.		
4. 39-1	...RLFTPGS...	
5. 57-1	...GLFYYGP...	

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From Poster #306; 4th International Meeting on Hepatitis C Virus and Related Viruses.

Witnessed & Understood by me, | Date | Invented by [signature] | Date 3/26/97